THERAPEUTICS OF NON-GONOCOCCAL URETHRITIS*†

BY

A. H. HARKNESS

Director, Venereal Diseases, Institute of Urology, University of London

Primary non-gonococcal urethritis of venereal origin is usually abacterial. This is also the case when the disease follows rectal coitus (Harkness, 1950). When organisms are present in the secretions in untreated cases the disease is more likely to have been caused by infections descending from a urethral stricture, the prostate, or lesions of the upper urinary tract. It can also be caused mechanically through the insertion of foreign bodies into the urethra. A diagnosis of bacterial (non-gonococcal) urethritis of venereal origin is, however, rarely made when thorough cleansing of the meatus to remove saprophytic organisms has preceded the taking of specimens for bacteriological examination. It should be noted that in women a bacterial urethral discharge is more frequently observed.

Treatment has changed completely since the introduction of the antibiotics derived from lower-grade fungi. Before this there was no specific therapy: we had to rely solely on urethro-vesical irrigations, which, when efficiently carried out twice daily, effected a cure in 2 to 8 weeks.‡ Residual non-gonococcal discharges were not formerly the problem they are to-day when penicillin therapy for gonorrhoea is so general: they were resolved unnoticed during the long irrigation treatment. Sulphonamide therapy, in my hands at least, is ineffective unless combined with *grande lavage*. Penicillin is useless. Indeed it is the ineffectiveness of penicillin in anything but the rapid elimination of gonococci that has convinced many workers of the actual existence of non-gonococcal urethritis.

* Read at a meeting of the M.S.S.V.D. on March 27, 1953.
† Received for publication April 2, 1953.

Material

I am here considering the effects of treatment in two series of cases.

(1) In the first series of 769 cases (including 33 cases of Reiter's disease), there was treatment with terramycin, aureomycin, chloramphenicol, streptomycin sulphate, dihydrostreptomycin, or streptomycin calcium chloride (Tables I and II).

‡ This type of treatment has not been abandoned: it is usually effective after failure with the antibiotics, and is particularly so in trichomonad infestations of the urethra.

TABLE I
TREATMENT IN FIRST SERIES OF 769 CASES

Antibiotic		Total Cases	Urethritis									Total Successes	
			Subacute			Acute			Post-gonococcal				
			Total	Successes		Total	Successes		Total	Successes			
				No.	Per cent.		No.	Per cent.		No.	Per cent.	No.	Per cent.
Terramycin		199	177	152	85	12	11	91	10	9	90	172	86
Aureomycin		302	289	185	64	5	2	40	8	4	50	191	63
Streptomycin	Sulphate ..	81	72	27	37	4	2	50	5	4	80	33	41
	Dihydrostreptomycin	51	48	17	35	1	0	—	2	0	—	17	33
	Calcium chloride	14	12	5	42	—	—	—	2	2	100	7	50
	Total ..	146	132	49	37	5	2	40	9	6	67	57	39
Chloramphenicol ..		89	83	27	32	1	1	100	5	3	60	31	36

TABLE II
TREATMENT OF 33 CASES IN FIRST SERIES WITH REITER'S DISEASE

Antibiotic	Total Cases	Reiter's Disease						Total Successes	
		Early*			Established				
		Total	Successes		Total	Successes			
			No.	Percent.		No.	Per cent.	No.	Percent.
Terramycin	9	4	4	100	5	2	40	6	67
Aureomycin	14	8	4	50	6	1	17	5	36
Streptomycin — Sulphate	5	1	0	—	4	1	25	1	20
Streptomycin — Dihydrostreptomycin	1	—	—	—	1	0	—	0	—
Streptomycin — Total	6	1	0	—	5	1	20	1	17
Chloramphenicol	4	1	0	—	3	0	—	0	—

*24 hrs' duration.

(2) In the second series the treatment of 156 cases with terramycin, aureomycin, streptomycin sulphate, and chloramphenicol was randomized (Table III).

TABLE III
RANDOMIZED SERIES OF 156 CASES

Antibiotic	Total Cases	Successes		Failures
		No.	Percent.	
Terramycin	39	34	87	5
Aureomycin	39	23	59	16
Streptomycin	39	15	38	24
Chloramphenicol	39	12	31	27
Total	156	84		72

Symptoms

For convenience of description the cases are classified as " Acute " and " Subacute " (Waelsch, 1904), but it must be remembered that there are intermediate types. In the acute variety of the disease, which usually has a short incubation period of 1 to 2 days, the discharge is profuse, often purulent, and indistinguishable from that in gonorrhoea ; it is sometimes haemorrhagic. The symptoms, usually severe, are pain on micturition, particularly at the end of the act, and frequency. The urine is muddy in both glasses and there may be terminal haematuria or blood-stained threads in the second glass. There also may be frank haematuria, as in cases in which there is disease of the upper urinary tract. In this type of infection there is a generalized cystitis (as in eight of my patients cystoscoped during the acute phase) similar in all respects to that in abacterial pyuria (Harkness and Henderson-Begg, 1948).

In subacute abacterial urethritis (the incubation period is anything from 3 to 50 days) the discharge is usually scanty and more often clear and viscid than purulent. Symptoms are mild or absent altogether.

It should be noted that urinary symptoms (dysuria and frequency) in both varieties of the disease often precede by one or more days the appearance of the urethral discharge.

Method

In the first series of 769 cases, 23 were acute and 681 subacute, and 32 were post-gonococcal (Table I). In five cases there was epididymitis before the beginning of treatment, in two others it followed sexual intercourse during treatment. The blood-borne complications of early (24 hrs' duration) and established Reiter's syndrome occurred in 33 cases (Table II). In this first series there was a previous history of gonorrhoea in 200 cases and of non-gonococcal urethritis in 159. The disease was maritally acquired in 151 cases, an indication that its common name, " husbands' clap ", is often justified. A history of intercourse at the time of a period (which had often started *during* the act) was obtained in 51 cases, and this led to the conclusion that the infective agent is at such times particularly liable to infect the sexual partner.

During antibiotic therapy and for at least a fortnight afterwards certain restrictions were imposed. Alcohol, sexual excitement, and excessive exercise were as strictly forbidden as in the pre-penicillin treatment for gonorrhoea.* It should be remembered that the drugs prescribed probably attack the infective agent through the urine as well as through the blood stream. Aureomycin, and terramycin appear in the urine in far higher concentrations than in the blood, and, as in abacterial urethritis the mucous membrane is the tissue most affected, the local action of the drug cooperates to a marked degree with the systemic. All patients were therefore advised to cut down fluid intake by half during the course and to pass urine frequently however small the amount to enhance the drug's local action. Fluids in large quantities were advised 24 hrs after the end of the course.

* No such restrictions are really necessary nowadays in the treatment of gonorrhoea, the contraction and cure of which need involve little but pleasure.

At the first examination a smear of the urethral discharge and a scraping were taken, the former being stained by Gram's stain and the latter by Giemsa's stain. Dark-ground examination for *Trichomonas vaginalis* was also carried out in a large number of cases. Cultures on ordinary media were not attempted in every case, but in most instances special cultures for pleuropneumonia-like organisms were made. Rectal examination to detect infection of the prostate, vesiculae seminales, or Cowper's glands was not made before the beginning of treatment and only afterwards when antibiotic therapy had failed to eliminate infection.* Urethroscopy was seldom performed before treatment except to demonstrate to students the inflamed mucosa in acute abacterial urethritis or the nodules in the Waelsch variety. It was subsequently carried out in all cases in which there was resistance to antibiotic therapy.

Congenital abnormalities were noted, and it is interesting to observe that in the first series there were 32 cases of hypospadias, 25 of which, being intrameatal in position, could only be detected by eversion of the lips of the external urinary meatus : there were two cases of epispadias. Very often a redundant prepuce completely covered the glans. In such cases the glans and the mucous membrane of the prepuce were moist thus making it difficult in subsequent examinations (unless there had been adjuvant treatment) to determine whether the discharge or threads in the urine came from the urethra or the preputial sac. Bathing of the glans twice daily followed after drying by the application of a bland powder was an essential adjuvant measure to eliminate secretion in such cases.

All patients were required to refrain from micturition for at least 3 hours before each visit, and after completion of treatment whenever possible an examination was arranged before the first morning micturition. The number of days for the discharge to cease, the symptoms to disappear, and the urine to become clear with no threads was noted in all cases.

As already stated, the second series was randomized, but in the first series terramycin and aureomycin were, when available, the drugs of choice.

The dosage of terramycin, aureomycin, and chloramphenicol was 0·5 g. 6-hrly (6 p.m., midnight, 6 a.m., and midday) for 4 days. In a small number of uncomplicated cases (usually of acute abacterial urethritis) in which resolution appeared incomplete on the 4th day, the course was extended for a further 2 days. Where there were blood-borne complications, the drugs in the same dosage were given for 10–14 days. Many failures with chloramphenicol led to the routine dosage being increased to 0·75 g. 6-hrly. With all varieties of streptomycin the dosage in uncomplicated cases was 1 g. dissolved in 4 ml. redistilled water once daily for 5 days, but in Reiter's disease 1 g. twice daily for 10–14 days was given.

* It had been noted that such procedure sometimes precipitates a mild and slowly resolving epididymitis, which is often mistaken, especially by the general surgeon, for tuberculous epididymitis.

Observations

Mild toxic reactions (such as looseness of the bowels and, less often, nausea) were frequently noted with chloramphenicol, aureomycin, and terramycin. Vomiting occurred in two nervous patients, one on aureomycin and the other on terramycin, necessitating the interruption of the course. Pruritus ani was also common but ulceration of the anus and also of the mouth occurred in only two patients, one after 20 g. aureomycin, and the other after 18 g. terramycin. Such ulceration never occurred in the many patients who had received as much as 28 g. of these drugs when a vitamin B complex was given at the same time.

In many cases Herxheimer-like reactions (exacerbation of signs and symptoms) were observed 24–48 hrs after the beginning of treatment, particularly in patients showing acute manifestations of the disease.

Trichomonads were demonstrated in 59 cases, and in one (the patient was a Negro who defaulted after 3 months) they persisted in the urethral discharge and prostato-vesicular secretions in spite of much treatment, including antibiotic therapy and urethro-vesical irrigations. It is difficult to determine whether the protozoon is a saprophyte or a pathogen, though it was found in the fourteen contacts who were examined. It would appear to be found more frequently since the introduction of antibiotic treatment and this may indicate a serious problem for the future.

Regarding the aetiology of the disease (Nicol and Edward, 1953), inclusions, mostly pleomorphic, were seen in a large number of our Giemsa-stained scrapings, and in 28 per cent. cultures for pleuropneumonia-like organisms were positive. Elementary and initial bodies of the virus of inclusion conjunctivitis were observed in only ten cases.

The role of pleuropneumonia-like organisms in causing these infections is still uncertain ; nevertheless their sensitivity to the drugs *in vitro* corresponds closely to the clinical response. It has been shown by various workers that these organisms are resistant *in vitro* to the sulphonamides and penicillin (Table IV, opposite).

TABLE IV

MINIMUM CONCENTRATIONS OF ANTIBIOTICS INHIBITING THE GROWTH OF PLEUROPNEUMONIA-LIKE ORGANISMS

Author	Date	No. of Strain	Type of Medium	Antibiotic					
				Penicillin (units/ml.)	Streptomycin Sulphate (mg./ml.)	Dihydrostreptomycin (mg./ml.)	Chloramphenicol (mg./ml.)	Aureomycin	Terramycin
Bushby	1953	6	Solid	>1,000	10	>50	12·5–25	25–50	0·2–2
Leberman, Smith, and Morton	1952	8	Fluid	—	—	—	—	—	0·1–0·5
	1950	15	Fluid	>1,000	0·1–15	15–200	15–100	25–200	—
Melén	1952	20	Not stated	>800	10	80	2·5–10	0·3–1·2	0·16–0·3

The drugs were tested by Bushby (1953) for ability to inhibit six strains isolated from patients in the first series. These strains were completely insensitive to penicillin and to the concentrations of dihydrostreptomycin and aureomycin that would be present in the blood of patients on the usual dosage; they were moderately sensitive to streptomycin and chloramphenicol, but very sensitive to terramycin. This high sensitivity to terramycin was also previously reported by Bushby (Edward, 1952). It will be noted that these strains were insensitive to the usual blood concentrations of all antibiotics except terramycin but sensitive to the concentrations that would be present in the urine except in the case of penicillin.

The sensitivities obtained with strains from my cases agree very closely with those found by Leberman and his collaborators (1950, 1952) in America, and by Melén (1952) in Scandinavia, except those reported for aureomycin by Melén who was presumably dealing with different strains.

Clinical observation during antibiotic therapy showed that in many cases the discharge ceased in 2–4 days, but in those that I have classed as failures it reappeared soon after the completion of the course. In such cases, however, cures were often obtained by giving a course of another drug. In subacute urethritis symptoms usually disappeared in 1–2 days, but in the acute variety they lessened gradually and disappeared altogether in 4–7 days. In many of the cases treated successfully, especially with terramycin or aureomycin, the urine was clear with no threads by the end of the 4-day course, though in some cases a few light mucous threads persisted for a week or 10 days before disappearing altogether. Persistence of heavy threads made it necessary to relegate the case to the list of failures. In some acute cases the discharge disappeared after a course of terramycin or aureomycin and the patient was rendered symptom-free, but a muddy and sterile urine persisted. In such cases adjuvant treatment of sandal-wood oil 15 m. three times daily cleared the urine in 3–6 days. (It must be remembered that sandal-wood oil alone is effective in the treatment of this type of infection.)

Persistence of threads may be due to urethral stricture of gonococcal or non-gonococcal aetiology. Strictures due to abacterial urethritis are wide and involve only the mucosa with no diminution in the calibre of the urethra: they can only be detected by urethroscopy. In patients with these wide strictures, dilatations (sometimes one only) will render the urine free from threads. In the first series of cases under review there were fifteen failures due to stricture, ten of which were of wide calibre.

Errors in Diagnosis.—Two cases showing abacterial urethral discharge and pyuria (they were not included in the present series) were wrongly diagnosed in the first place. Tubercle bacilli were found in the urine in both and the patients were passed to surgical colleagues for further investigation and treatment.

Three further cases (vesical diverticulum, calculous pyonephrosis, prostatic calculi) each showing descending bacterial non-gonococcal urethral discharges were also transferred.

In one case of Stevens-Johnson syndrome, there was a profuse abacterial urethral discharge, severe dysuria, conjunctivitis, and polyarthritis. This was wrongly diagnosed as Reiter's disease until a generalized erythema iris developed 10 days after a course of aureomycin. It is interesting to note that with cortone treatment the skin lesions rapidly disappeared, but on omission of the maintenance dose the arthritis relapsed.

Criteria of Cure

Before a patient can be declared cured there should be no urethral discharge and the urine should be clear with no threads. Most of the cases under review were observed for at least a month after antibiotic therapy, during which time at least one examination was made before

the first morning micturition and bath. After treatment, a few threads in the first glass of urine (often due to resolution processes) sometimes persisted for a few days, and if these did not disappear during the first week of observation thorough investigations were made and the case was classified as a failure. In some cases a clear secretion not containing leucocytes remained with a urine either clear with no threads or with a few light mucous threads which under the microscope revealed only an occasional leucocyte. Such cases were regarded as cured when the threads disappeared without further treatment.

Examination of the vesiculo-prostatic secretion and urethroscopy were carried out only in selected cases. (For example, urethroscopy should always, in my opinion, be carried out in cases in which there is a previous history of gonorrhoea from the pre-sulphonamide era.) Alcohol, violent exercise, and sexual intercourse with condom protection were allowed after a 14-day observation period. It may also be noted that during the observation period efforts were made to examine and treat all contacts.

In assessing results it is sometimes difficult to differentiate between relapse and re-infection. In some cases of apparent cure the antibiotic may merely have put the infective agent to sleep, only to be reactivated by additional factors such as alcohol and sexual trauma. This does occasionally occur, but most of such cases are, in my opinion, re-infections. I have had several women under my care who were known to have infected as many as five men with the disease. I have also observed many patients (three over a period of two years) who had acquired the disease maritally, and who remained subsequently free from infection as long as they were protected by a condom during intercourse. Neglect of this was followed by an abacterial urethritis : in two cases this was always associated with conjuncitivits and polyarthritis. Several years ago one of these patients, at my request, as I wished to carry out certain investigations, undertook marital intercourse without protection. Infection was evident in 7 days, and, after I had taken specimens, he was cured with aureomycin. Nowadays I always treat the female partner with a course of terramycin or aureomycin and also advise douching for 2 days after each period ; 41 contacts of patients in the present series were examined and thus treated and in only one was a subsequent re-infection reported. In 28 out of 55 cases (51 per cent.) vaginal and/or cervical swabs gave positive cultures for pleuropneumonia-like organisms : cultures were negative after treatment in all but two cases. There were, however, two failures (one with streptomycin, and the other with chloramphenicol) where cultures were subsequently negative, one after treatment with terramycin, the other with aureomycin.

Results

Results in the first series of 736 cases show the following cure rates : terramycin 86·5 per cent. ; aureomycin 63 per cent. ; streptomycin 39 per cent. ; chloramphenicol 36 per cent. It was surprising to note (Table I, p. 134) that streptomycin calcium chloride showed a 50 per cent. success ratio, but the total number of cases thus treated was too small for any definite conclusions to be drawn.* It will be seen that terramycin and aureomycin gave a higher percentage of cures than any of the other drugs.

Two patients resistant to treatment contracted gonorrhoea during the observation period, but were cured of the gonorrhoea and the non-gonococcal urethritis after one injection of 600,000 units of procaine penicillin. Inoculation of gonorrhoea may be something to bear in mind in the treatment of failures.

Failure with one drug does not necessarily connote failure with any other ; in spite of what experts have to say about cross fixation. Failures with streptomycin or chloramphenicol often react favourably to terramycin or aureomycin. Unfortunately the drugs used in the first and larger series, particularly terramycin and aureomycin, were not continually available, and it was therefore difficult to gain any statistical evidence of the therapeutic superiority of one over the other. However, as the Tables show, terramycin gave a much higher percentage of cures. It was successful also in 24 out of 31 cases in which aureomycin had previously failed, the reverse happening in only two out of six cases.

In three primary cases in the first series, there were subsequent blood-borne complications during courses of aureomycin (this was never so with terramycin), and in two of these terramycin was immediately and effectively prescribed (but it was, unfortunately, not available for the third case). One of the patients had a profuse mucopurulent discharge of 2 days' duration with dysuria and a muddy urine in the first glass only, but after 2 g. aureomycin the discharge became more profuse and the urine muddy in both glasses. At first this was thought to be a Herxheimer-like reaction, but instead of diminishing the signs persisted and on the fourth day (on completion of the aureomycin

* A further and more extensive trial of this drug is now in progress.

TABLE V
CALCULATION OF χ^2

Drug	Observed ($m + X$)		Expected (m)		Difference (x)		$\chi^2 = S\left(\frac{x^2}{m}\right)$	
	Cured	Not Cured	Cured	Not Cured	Cured	Not Cured	Cured	Not Cured
Terramycin ..	34	5	28·5	10·5	5·5	−5·5	$\frac{(5·5)^2}{28·5} = 1·061$	$\frac{(-5·5)^2}{10·5} = 2·862$
Aureomycin ..	23	16	28·5	10·5	−5·5	5·5	$\frac{(-5·5)^2}{28·5} = 1·061$	$\frac{(5·5)^2}{10·5} = 2·862$
Total Patients..	57	21	Total: $\chi^2 = 7·846$					

course) the temperature registered 101° F. and there was bilateral conjunctivitis with arthralgia and myositis. An 8-g. course of terramycin was prescribed and within 24 hrs there was a complete and dramatic recovery, all signs of disease having disappeared, and there was no relapse.

Fourteen early cases of Reiter's disease were treated solely with the drugs under review (Table II, p. 135): four with terramycin* (all successes); eight with aureomycin (four successes); one with chloramphenicol (failure); one with streptomycin (failure).

In nine established cases of Reiter's disease, two out of five were cured with terramycin (one after failure with aureomycin); one out of six responded to aureomycin; one out of four responded to streptomycin sulphate. Treatment with dihydrostreptomycin failed in one case.

In established cases of Reiter's disease, the ideal treatment, in my opinion, is fever therapy combined with terramycin or aureomycin. Of eight cases treated in this manner (they are not included in the present series), four reacted favourably to terramycin and three of the remainder to aureomycin.

Statistical Analysis of the Randomized Series

The results obtained in the first series of cases indicated strongly that terramycin was more potent than aureomycin and much more potent than streptomycin or chloramphenicol. To test this indication by a method the results of which could be submitted to statistical analysis a further comparison was made. Patients coming for treatment were " randomized " ; that is, the first four patients were assigned to treatment with terramycin, aureomycin, streptomycin sulphate, or chloramphenicol, according as a ticket marked T, A, S, or C was drawn at random from a coat pocket. The tickets were returned to the pocket and the same procedure was followed for each group of four patients, until 39 patients had been allotted to each of the four drugs. Thus any inclination on the part of the clinician to give a severe case the drug that was thought to be best was avoided, as also was any inclination to give a mild case the drug that might seem to be a certain cure. The results from this randomized series may be seen in Table III. The criteria of cure have already been stated.

The data were submitted to analysis by Fisher's method of determining values for χ^2. This is an estimate of the divergence from what one would have expected to happen if two drugs had been of equal potency; *e.g.*, with terramycin and aureomycin 57 patients were cured and 21 patients were not cured. In fact, 34 patients were cured with terramycin and only 23 with aureomycin, not a half of 57 with each as might have been expected if the drugs had been equally potent. The calculation of χ^2 from these figures gives a measure of the probability that the observed difference was due to chance (Table V).

The Table of χ^2 (Mathematical Tables for Statistical Analysis) gives the value 6·635 ($d/f = 1$) for a probability of 0·01 that the difference in the results from the two drugs is due to chance. Since 7·846 is larger than 6·635, the probability that this difference is due to chance is less than 1 in 100. Therefore there is very good evidence that the difference is significant, *i.e.*, that terramycin really is more effective than aureomycin.

Other comparisons of different pairs of drugs are given in Table VI.

TABLE VI
DRUGS STATISTICALLY COMPARED

Drugs	χ^2	P = probability that the difference is due to chance
Aureomycin and Streptomycin Sulphate	3·284	Slightly greater than 0·05
Streptomycin Sulphate and Chloramphenicol	0·510	Greater than 0·5
Aureomycin and Chloramphenicol	6·272	Much less than 0·05 and only slightly greater than 0·01

* One of the terramycin-treated cases was a second attack in which the only manifestation was a unilateral iritis.

The probability of $P = \cdot 05$ (*i.e.*, 1 in 20) is generally considered significant; that is, it is fairly safe to conclude that values of χ^2 for values of P less than 0·05 indicate a significant difference in treatments, whereas values of χ^2 for values of P greater than 0·05 indicate no significant difference. Thus the difference between aureomycin and streptomycin sulphate is on the verge of significance. A larger number of patients might have shown that it was indeed significant. The difference between streptomycin and chloramphenicol is obviously insignificant, but χ^2 was determined to see how large P was with these figures. The difference between aureomycin and chloramphenicol is clearly significant, since P is much less than 0·05 and only slightly larger than 0·01. The differences between terramycin and streptomycin or chloramphenicol are obviously significant without calculation.

Thus the statistical analysis of the results from the "randomized" patients indicates that terramycin is more potent than any of the other three drugs; and that aureomycin is more potent than chloramphenicol and probably more so than streptomycin sulphate, especially in view of the finding of no significant difference between streptomycin sulphate and chloramphenicol.

It is interesting to note that the drug that is the most active in the test tube is also the most active clinically. Of the five antibiotics used, only terramycin is sufficiently active *in vitro* to give concentrations in the blood (or tissues) throughout the course of treatment. All the antibiotics, however, with the exception of penicillin, are sufficiently active to make the urine bacteriostatic: with these the therapeutic effect would seem to be primarily local.

Summary

(1) The effect of treatment with terramycin, aureomycin, chloramphenicol, streptomycin sulphate, dihydrostreptomycin, and streptomycin calcium chloride on non-gonococcal urethritis has been investigated in two series of 769 and 156 cases respectively.

(2) Terramycin, aureomycin, and chloramphenicol were given in a dose of 0·5 g. 6-hrly for 4 days; when blood-borne complications were present the treatment was continued for 10–14 days. The dose of chloramphenicol was later increased to 0·75 g. 6-hrly as the lower dose was so often ineffective. The streptomycin preparations were given in a dose of 1 g. in 4 ml. water once daily for 5 days, and twice daily for 10–14 days in cases of Reiter's disease.

(3) Aureomycin and terramycin in particular attain a high concentration in the urine, and the therapeutic effect can be enhanced by restricting fluids by one half and instructing the patient to pass urine frequently.

(4) Infection with *Trichomonas vaginalis* was present in 59 cases and was resistant to the antibiotic treatment. Pleuropneumonia-like organisms were seen in preparations from a large number of cases and were isolated in culture in 28 per cent. of them: six strains were completely insensitive to dihydrostreptomycin and aureomycin in concentrations that would be present in the blood, moderately sensitive to streptomycin and chloramphenicol, and very sensitive to terramycin *in vitro*. Elementary bodies of inclusion conjunctivitis type were seen in ten cases.

(5) In cases which responded to treatment, the discharge ceased in 2–4 days and symptoms disappeared in 1–7 days.

(6) The following cure rates were obtained in the first series: terramycin 86·5 per cent.; aureomycin 63 per cent.; streptomycin 39 per cent.; chloramphenicol 36 per cent. A cure was also obtained with terramycin in 24 out of 31 cases which had not responded to aureomycin. The apparent superiority of terramycin was confirmed in the second series of cases by statistical analysis, the following cure rates being obtained: 87 per cent., 59 per cent., 38 per cent., and 31 per cent. respectively.

(7) Cases of Reiter's disease are best treated with fever therapy combined with terramycin or aureomycin.

My thanks are due to my colleagues (Drs. Mascall, Chesney, Macdonald, Haber, Baker, and Lamb) at St. Paul's Hospital, London; to my Charge Nurse, Mr. J. J. Croxford, for much clinical and laboratory assistance; to Dr. K. H. Coward for the statistical analysis of the randomized series; and to Dr. G. Hobby of Charles Pfizer, Ltd., for the very liberal supply of terramycin.

REFERENCES

Bushby, S. R. N. (1953). Personal communication.

Edward, D. G. ff. (1952). *British Journal of Venereal Diseases*, **28**, 89.

Harkness, A. H. (1950). "Non-Gonococcal Urethritis", Livingstone, Edinburgh.

——, and Henderson-Begg, A. (1948). *British Journal of Venereal Diseases*, **24**, 50.

Leberman, P. R., Smith, P. F., and Morton, H. E. (1950). *J. Urol., Baltimore*, **64**, 167.

——, ——, ——(1952). *Ibid.*, **68**, 399.

Melén, B. (1952). *Acta path. microbiol. scand.*, **30**, 98.

Nicol, C. S., and Edward, D. G. ff. (1953). *British Journal of Venereal Diseases*, **29**, 141.

Waelsch, L. (1904). *Arch. Derm. Syph. Wien*, **70**, 103.